

To be printed on hospital headed paper

PATIENT INFORMATION SHEET

Version 1.0, 20th December 2016

Study name: MICRObiota, inflammatory Environment, clinicAI and Radiomic features as predictors of Normal tissue response in radiotherapy for prostatE and head-and-neck canceR. (MICRO-LEARNER)

Ethics Approval Reference: INT 11-17

**This module,
that will be given to you with a reasonable advance with respect to your final decision,
provides you with the essential information about the clinical study you are asked to participate.
It is important that you read this information and discuss it with your doctor
before signing the consent to participation in the study
Only Patients who accept will be enrolled in the study.
Patients can withdraw their consent at any time.**

MICRObiota, infLammatory Environment, clinicAI and Radiomic features as predictors of Normal tissue response in radiotherapy for prostatE and head-and-neck canceR. (MICRO-LEARNER)

Dear Patient,

You are invited to take part in a research study. We would like to explain to you why the research is being done and what it will involve for you. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if anything is not clear or if you need more information. Take time to decide if you wish to take part.

What is the purpose of this study?

The purpose of this study is to try to predict which patients who receive radiotherapy are more likely to have side effects than others. Approximately half of all cancer patients receive radiotherapy as part of their cancer treatment. The dose of radiation given, however, is limited because of a risk of damaging the healthy cells that surround the tumour. Patients vary in how they react to radiation. About 5% of patients (5 out of every 100) are sensitive and at risk of having side effects.

In recent years, researchers have developed predictive models and biological tests to try to identify before the start of treatment those patients who are very sensitive. However, these methods are not yet ready to use in the clinic so radiation doses for all patients are currently limited by the doses the most sensitive patients can have.

The observational study MICRO-LEARNER addresses the issue of individual sensitivity to radiation with an innovative approach. In particular, we propose to study the composition of the gut and salivary microbiome at the individual level. The microbiome is the population of microorganisms that live in balance within our organism. There are some studies that show that these microorganisms are important in determining the individual sensitivity to radiation. The main purpose of MICRO-LEARNER is to determine whether there is an association between the type of microbiome of single individual and his/her probability of exhibiting side effects of radiotherapy.

We hope that results from this study will improve current predictive models and biological tests to predict how a patient will respond to radiotherapy. If we are successful, then in future we could identify the 'radiosensitive' patients before they start their radiotherapy

In the long term, our ultimate hypothesis is that information on the individual microbiome before radiotherapy could allow a modification of the microbiome itself in particularly susceptible patients, thus reaching an advantage for future patients. Sensitive patients could potentially be safely and effectively treated after modification of their microbiome, and other patients could be treated with more radiation. This should reduce side effects for all patients, improve quality of life and potentially increase the number of patients successfully treated for their cancer.

Why have I been chosen?

You are invited to take part in this study because you were recently diagnosed with prostate or head-and-neck cancer and your doctor has recommended that you should receive radiotherapy. The MICRO-LEARNER study needs 400 patients in total to take part. All patients will be enrolled at the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan

Do I have to take part?

No, it is entirely voluntary. If you decide to take part, please keep this information sheet and sign a consent form to show you agree to participate. We will also ask your permission to tell your family doctor that you are taking part in the study. If you do take part, you can withdraw at any time and without giving a reason. A decision to withdraw, or a decision not to take part, will not affect in any way your treatment or the standard of care you receive now or in the future.

What will happen to me if I do take part?

If you decide to take part in this study, you will be seen by a member of the research team at the beginning of your radiotherapy treatment who will then ask you to complete some questionnaires asking about symptoms you may be experiencing before you start your radiotherapy treatment and about your general well-being. You will then be asked to complete the same questionnaires again when your radiotherapy is finished and then at routine follow-up appointments at least twice a year for at least three years after your treatment. This is a practical and reliable way for us to measure and record the effects of your radiotherapy treatment. These questionnaires should preferably be completed in the clinic (but could be done at home) and take no more than 20 minutes to complete each time

If you are receiving treatment for prostate cancer, we will ask you to collect two fecal samples for the analysis of your gut microbiome. They are to be collected at home using a kit that will be provided by the healthcare staff. One sample will be collected before the radiotherapy and one at the end of the treatment. We will also ask you to provide us with three blood samples, one before the beginning of radiotherapy, one after two weeks of treatment, and one at the end of the radiotherapy. Each time, we would like to take a maximum 20 ml of blood, which is less than three tablespoons and similar to the amount taken for routine blood-testing. Then, you'll be asked to perform a multi-parametric magnetic resonance one year after the end of the radiotherapy treatment. This is a very advanced imaging examination that will allow us to investigate how your tissues have responded to radiotherapy.

If you are receiving treatment for a head-and-neck cancer, we will ask you to collect two samples of saliva for the analysis of your salivary microbiome using a kit that will be provided by the healthcare staff. One sample will be collected before the radiotherapy and one at the end of the treatment. We will also ask you to provide us with three more saliva samples, one before the beginning of radiotherapy, one after two weeks of treatment and one at the end of the radiotherapy, and a blood sample before treatment. we would like to take a maximum 20 ml of blood, which is less than three tablespoons and similar to the amount taken for routine blood-testing.

If you have an oropharynx cancer, you will also be asked to perform a multiparametric magnetic resonance after two weeks of radiotherapy. This is a very advanced imaging examination that will allow us to investigate how your tissues are responding to radiotherapy.

For all patients

Apart from the short time involved and the minimal discomfort associated with giving blood and collecting fecal/saliva samples, there should be no pain, distress or inconvenience caused to you by taking part in the MICRO-LEARNER study. Your blood/fecal/saliva sample will be coded using a unique study number so that no one outside the study can identify you from it. All samples will be stored and analyzed locally. The results of these tests will not be fed back to you or your doctor.

It may be possible to use your blood/saliva samples for other tests in the future. We would like to store your samples for future medical research on this or a related project. With your permission, the side effects

information and imaging scans could also be used anonymously (linked with a unique study identifier) in future studies. Future research may be carried out at academic institutions, hospitals or by commercial companies involved in cancer research worldwide. Please be aware that this could mean that doctors and scientists in other countries might use your blood/saliva samples and medical data. However, the data will not contain any personal information so you could not be identified. Please read the section below called *'Will my taking part in the study be kept confidential?'* All new research work planning to make use of samples and/or data will be subject to ethical approval by this Foundation.

Would participating in this study be of any benefit to me?

There will be no direct benefit to you.

Would participating in this study be harmful to me?

MICRO-LEARNER is an observational study so your treatment will not change by choosing to take part in this study. As indicated above, you will be asked to complete some questionnaires and to give a blood/saliva/fecal samples. Potential harms of taking blood are haematoma or extremely rarely impairment of nerves. If you are harmed by taking part in this research project, the insurance policy stipulated by this Foundation guarantees a specific coverage, in accordance with current legislation

Will my taking part in the study be kept confidential?

All information will be kept strictly confidential and your name will not appear on any publications resulting from the study. Your medical notes will be seen by authorised members of the research team at this institute, so that they can collect information needed for the MICRO-LEARNER study. You will be given a unique MICRO-LEARNER study number, which will be used together with your initials and date of birth on any forms that the research staff fill in. Samples will be coded with the unique MICRO-LEARNER study number and kept anonymously which means that the laboratory researchers who are carrying out any tests on your sample cannot identify you. All information about you will be treated as strictly confidential and nothing that might identify you will be revealed to any third party.

What happens to my samples and information if I decide to withdraw?

You can withdraw at any time and without giving a reason. If you decide to withdraw your coded blood samples and information will be retained for use in this study and for future medical research unless you specifically request otherwise. If specifically requested, your samples will be destroyed and your medical information removed from the MICRO-LEARNER database.

How will I know the results of the study?

When the study is complete, the results will be published in medical and scientific journals and also presented at medical and scientific meetings. All data are anonymised (i.e. your name will not be disclosed in journals or at presentations).

Who is organising and funding the research?

This study is being carried out by a network of medical doctors and scientists from the Fondazione IRCCS Istituto Nazionale dei Tumori. It is funded by the Scientific Directorate of this Foundation. The study leader is Prof. Riccardo Valdagni.

Insurance coverage.

Given the observational nature of the study, otherwise being clinical activity, the insurance policy stipulated by this Foundation guarantees a specific coverage, in accordance with current legislation.

Guarantees for the protection of the Patient participating in the clinical trial.

The study was approved by the independent Ethics Committee at the National Cancer Institute in Milan.

Biological samples will be processed, stored and analyzed under the responsibility of:

Dr. Loris De Cecco, Department of Experimental Oncology and Molecular Medicine

and Dr. Nadia Zaffaroni, Department of Molecular Pharmacology

Fondazione IRCCS Istituto Nazionale dei Tumori, Via Amadeo 42, Milan

Your decision as to whether or not to take part in this study is completely of your free will. This means that if you decide not to take part in this study this will not affect the care you receive at this institution.

A copy of this Information Sheet and a copy of any possible Consent will remain in the possession of the Patient who agrees to participate in the study.

Information and demonstration of consent to the processing of personal data

(following resolution no. 52 of 24/7/2008 Guidelines for the processing of personal data in clinical trials of drugs)

Holder of the treatment of your personal data and related goals

Fondazione IRCCS Istituto Nazionale dei Tumori will treat your personal data, especially those related to your health, and only to the extent that they are essential in relation to the purpose of the study, exclusively for the purpose of fulfillment of the study.

The up-to-date list of data managers for the patients participating in the study and of all subjects that treat your data - including laboratories for analysis - are available and on your request the clinician who is taking care of you will be able to provide it.

Nature of data

The doctor who will undertake the study will identify you with a code: the data relating to you collected during the study, except your name, will be recorded, processed and stored together with this code and with your date of birth, gender, weight and height. Only your doctor and any authorized parties can connect this code to your name.

Data processing procedure

Your data, also processed by electronic means, will be distributed only in strictly anonymous form, e.g. through scientific reports, statistics and scientific meetings.

The data, also processed using electronic instruments, will be released only in anonymous form, such as through scientific publications, statistical reports and presentations at scientific conferences.

Your participation to the study, in agreement with regulation on clinical trials involving drugs, entails that any persons employed for monitoring and verification, the Ethics Committee and any regulatory authorities (from Italy or from foreign country) will have direct access to data and medical records to verify the study procedures and / or data, in such a way as to guarantee the confidentiality of your identity.

Exercise of rights

Under Article 7 of Italian Legislative Decree no. 196/2003 (the so-called "Code of privacy"), you are entitled to exercise your right (such as access your personal data, integrate, correct them, oppose to their processing for legitimate reasons) addressing directly to the experimental center (Prof. Valdagni, Radiation Oncology 1, 02 23903034).

You may terminate at any time, without giving any reason, your participation in the study: in this case, the biological samples relating to you will be destroyed. Additionally, no further data relating to you will be collected, subject to the use of those data already collected to determine, without altering them, the results of the research.

By providing this consent, you authorize the handling of biological samples and health information that concern you for the purposes of the study by any persons involved in the research (health personnel, data managers, statisticians, inspection staff of regulatory agencies and those authorized by the study protocol and / or by current laws). In this case, any information concerning you will, in the event, be published only in anonymous form, carefully and rigorously avoiding any detail that may in some way allow third parties to trace your identity. In addition, the data relating to you will be stored in accordance with the protection measures foreseen by the Law.

What should I do now?

It is up to you to decide whether to take part. Please think about what the study involves and discuss it with your friends and family. Your research doctor or nurse will be happy to answer any questions you might have. When you decide, please let your research doctor or nurse know. You will be asked to sign a consent form and will be given a copy to keep together with this information sheet. Please keep these safe. If, at any time, you have any questions about the study you can contact the MICRO-LEARNER research doctor or nurse using the details below.

We remind you that your decision as to whether or not to take part in this study is completely of your free will. This means that if you decide not to take part in this study and not to sign the Informed Consent this will not affect the care you receive at this institution.

Research nurse: <to be inserted>

Phone number: <to be inserted>

Email address: <to be inserted>

Thank you for considering helping with our research.

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**INFORMED CONSENT
TO PARTICIPATION IN THE BIOLOGICAL STUDY
TO PERSONAL DATA PROCESSING**

*This form must be signed by you only if you decide to participate in the clinical trial.
It is important that you have discussed in depth
with your doctor before signing this consent,
including discussion of the Patient Information Sheet describing this trial.
Only Patients who accept this Consent will participate in the study.
A Patient can withdraw his consent at any time.*

I confirm that I have read and understood the MICRO-LEARNER patient information sheet for the above study and have a copy to keep. I was able to consider the information with the doctor, ask questions and had them answered satisfactorily.

I give my free and informed consent:

- to participate in this clinical trial
- to processing of my personal and medical data, in paper and electronic format, in compliance with the regulations in force, inter alia of Decree 196/2003 and subsequent modifications to integration of the consent already signed by me to processing of my sensitive data at the National Cancer Institute in Milan
- to the collection, storage, and use of biological samples to carry out research following the previously detailed conditions

Any resolution that is not specified in the attached information sheet cannot be made, unless a new Ethics Committee's approval is obtained. In this case the Ethics Committee will decide whether it is necessary to obtain a new consent from me.

The results of the analysis will only be published in anonymous form and aggregated with the results of the analysis of other patients. I have the right to request the destruction of samples, if not already used, and only for the time when this is technically possible, especially until they have been completely anonymized.

There will be no information available to me or to my doctors about the results of the tests on my biological samples, given their experimental character, but I may ask (even now) to be informed about the results of this biological study, as well as those of the main clinical trial.

Signature of the researcher taking the consent

Printed name

Date:/...../.....

Signature of the patients

Printed name

Date:/...../.....

Signature of Legal Representative or Tutor (if applicable)

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Printed name

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Date:/...../.....

Signature of Witness (if applicable)

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Printed name

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